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# Correspondence

## Do Penicillins Really Increase the Frequency of a Rash When Given During Epstein-Barr Virus Primary Infection?

To the Editor—Based on old medical reports, it is commonly accepted that the acute phase of Epstein-Barr virus (EBV) infection (henceforth called "AEI") induces a transient hypersensitivity to β-lactams, resulting in a rash in up to 90%–100% of patients inadvertently given penicillin derivatives (PDs) [1–3]. As a result, such a drug-induced reaction has become suggestive of EBV primary infection [4].

Since 2008, our group has carried out a prospective, noninterventional survey on AEI. We gathered the medical records of all inpatients and outpatients referred to our regional hospital (1250 beds) with this diagnosis, combining cases of all ages from all departments. We only retained cases with clinical and biological evidence for AEI, for which a diagnosis was validated by the physician together with results showing positive IgM (with or without IgG) anti-Viral Capsid Antigen and negative anti-Epstein-Barr Nuclear Antigen antibodies. All clinical, biological, and therapeutic data (before, during, and eventually after passage in our institution) were carefully analyzed to assess the potential link between the occurrence of a rash and the use of antibiotics.

Over the last 5 years, we identified 239 cases of AEI, of which 184 had fully documented medical records. Overall, 34 of 184 patients (18.5%) experienced a rash that was either maculopapular/morbilliform (80%), generalized (52%), pruritic (44%), hive-like (18%), or purpuric (15%). Patients with rash were significantly younger, less likely to have severe dysphagia, and thus to receive systemic corticosteroids (Table 1). Among all the patients evaluated, 103 were exposed to at least 1 PD (mostly amoxicillin [83%] plus a β-lactamase inhibitor [41%]): 5 developed a rash prior to the antibiotic initiation, 6 developed a rash within 48 hours, and 5 additional cases occurred a median of 8 days after antibiotic treatment initiation.

Overall, the probability to experience a rash was similar between patients exposed and those not exposed to any PD (16/103 vs 18/81, respectively; $P = .3$). In our experience, systemic corticosteroids (SCs) were frequently prescribed during AEI and were associated with a decreased rash occurrence (odds ratio = 0.37 [95% confidence interval, .14–.94], $P = .04$). This may be due to their potency for shortening or attenuating the clinical signs of AEI. To avoid a potential bias between the use of SCs, PDs, and rash recognition, we stratified our analyses by SC exposure. As a result, we showed that the use of PDs was not correlated with rash, regardless of exposure to SC ($P = 1.0$ and $P = .5$ for SC exposed/nonexposed subgroups, respectively).

Because the patients who experienced a rash after they were given PDs were not skin tested for β-lactam allergy, we cannot rule out that drug hypersensitivity was involved in some cases. Nevertheless, our medical evidence–based data suggest that with current PDs, rash that occurs during acute EBV infection is likely not as common as perceived and

**Table 1. Characteristics and Therapeutics of Patients With Acute Epstein-Barr Virus Infection According to Cutaneous Involvement**

| Variable[a] | Patients With Rash (n = 34) | Patients Without Rash (n = 150) | *P* Value[b] |
|---|---|---|---|
| Age, y, median | 11.9 | 18.0 | .03 |
| Male sex | 17 (50) | 81 (54) | .71 |
| White ethnicity | 27 (79) | 135 (90) | .14 |
| Previous history of β-lactam allergy | 2 (6) | 8 (5) | 1 |
| Highest recorded temperature, °C, median | 39.0 | 39.1 | .48 |
| Pharyngitis | 25 (74) | 115 (77) | .87 |
| Cervical lymphadenopathy | 21 (62) | 115 (77) | .12 |
| Hepatomegaly | 6 (18) | 18 (12) | .40 |
| Splenomegaly | 10 (29) | 36 (24) | .52 |
| Severe dysphagia | 6 (18) | 58 (39) | .03 |
| Hospitalization | 26 (76) | 111 (74) | .83 |
| Antibiotics | | | |
| Any antibiotic | 17 (50) | 94 (63) | .18 |
| Any penicillin derivatives | 16 (47) | 87 (58) | .26 |
| Amoxicillin | 14 (41) | 71 (47) | .57 |
| Amoxicillin + β-lactamase inhibitor | 5 (15) | 37 (25) | .26 |
| Systemic corticosteroids | 6 (18) | 56 (37) | .03[c] |

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] *P* values were calculated with the use of Fisher exact test or a $\chi^2$ test for categorical data, and Wilcoxon rank-sum test for continuous data reporting median values.

[c] Remained the only significant risk factor associated with rash occurrence when covariates with a *P* value <.10 were entered into a multivariate logistic regression model.

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obviously much lower than originally reported. Moreover, our findings are corroborated by 2 other recent reports [5, 6]. Therefore, such a relationship should no longer be taught to medical students as a dogma. Continued surveillance to clarify the true incidence of rash attributable to antibiotics is warranted in this setting.

## Notes

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